

Human Perivascular Stem Cells Show Enhanced Osteogenesis and Vasculogenesis with NELL-1 Protein.

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Public Summary:

In this study the authors describe a novel strategy for stem cell-based bone regeneration. The authors demonstrate that Perivascular Stem Cells (PSCs), purified from human fat and combined with the protein NELL-1, can efficiently form bone nodules when implanted in a mouse muscle pocket. The novelty of this study resides in the injection of stem cells directly purified from fat without extensive manipulation in the laboratory, as conventionally done for Mesenchymal Stem Cell-based cell therapy, which could lead to loss of regenerative potential or cell transformation. Furthermore, the authors show that NELL-1 is a novel growth factor able to specifically stimulate bone and blood vessel formation without the side effect observed with the conventional bone-stimulating growth factor BMP2 (fat differentiation, inflammation, uncontrolled bone formation). This novel and safer stem cell application for bone regeneration based on the combination of non-cultured PSC and NELL-1 holds promise as a future cell-and- growth-factor-based therapeutic.

Scientific Abstract:

An ideal mesenchymal stem cell (MSC) source for bone tissue engineering has yet to be identified. Such an MSC population would be easily harvested in abundance, with minimal morbidity and with high purity. Our laboratories have identified perivascular stem cells (PSCs) as a candidate cell source. PSCs are readily isolatable through fluorescent activated cell sorting from adipose tissue and have been previously shown to be indistinguishable from MSCs in phenotype and differentiation potential. PSCs consist of two distinct cell populations: [1] pericytes (CD146+, CD34-, CD45-), which surround capillaries and microvessels, and [2] adventitial cells (CD146-, CD34+, CD45-), found within the tunica adventitia of large arteries and veins. We previously demonstrated the osteogenic potential of pericytes by examining pericytes derived from human fetal pancreas, and illustrated their in vivo trophic and angiogenic effects. In the present study, we used an intramuscular ectopic bone model to develop the translational potential of our original findings using PSCs (as a combination of pericytes and adventitial cells) from human white adipose tissue. We evaluated human PSC (hPSC)-mediated bone formation and vascularization in vivo. We also examined the effects of hPSCs when combined with the novel craniosynostosis-associated protein, NELL-1 (Nel-like Molecule I). Implants consisting of demineralized bone matrix putty combined with either NELL-1 (3microg/microL), hPSC (2.5 x 10⁵ cells), or hPSC+NELL-1 were inserted in the bicep femoris of SCID mice. Bone growth was evaluated using micro computed tomography, histology and immunohistochemistry over 4 weeks. Results demonstrated the osteogenic potential of hPSCs and the additive effect of hPSC+NELL-1 on bone formation and vasculogenesis. Comparable osteogenesis was observed with NELL-1 as compared to the more commonly used Bone Morphogenetic Protein (BMP)-2. Next, hPSCs induced greater implant vascularization than unsorted stromal vascular fraction (SVF) from patient-matched samples. Finally, we observed an additive effect on implant vascularization with hPSC+NELL-1 by histomorphometry and immunohistochemistry, accompanied by in vitro elaboration of vasculogenic growth factors. These findings hold significant implications for the cell/protein combination therapy hPSC+NELL-1 in the development of strategies for vascularized bone regeneration.

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